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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Signed *A. B. Jones*

Dated 3 August 2001

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The
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Request for grant of a Patent Form 1/77

Patents Act 1977

1 Title of invention

TREATMENT OF WOUNDS

- 1 Please give the title of the invention

2 Applicant's details

- ☒ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country (and State of incorporation, if appropriate)

UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address
RAMSGATE ROAD
SANDWICH
KENT

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
(if known)

6892673001

2d, 2e and 2f:

If there are further applicants
please provide details on a separate
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☐ **Second applicant (if any)**

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Country (and State of incorporation, if appropriate)

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3

An address for service in the United
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3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☒ No ☐ ➡ go to 3b



Please give details below

Agent's name

~~DR. RICHARD C. SEWELL~~

Agent's address

~~PFIZER LIMITED~~

~~RAMSGATE ROAD~~

~~SANDWICH~~

~~KENT~~

Postcode CT13 9NJ

Agent's ADP
number

-7964 992001

Urquhart - Dykes + Lord
Tower House
Merrion Way
LEEDS
LS2 3PA

See
S1/77

3b:

If you have appointed an agent,
all correspondence concerning
your application will be sent to
the agent's United Kingdom
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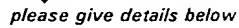
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4 Agent's or applicant's
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5 Claiming an earlier application date

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Yes ☐ No ☒ ➡ *go to 6*



 filing date

 and the Section of the Patents Act 1977 under which you are claiming:

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6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number (if known)	Filing date (day.month.year)
31		

7

The answer must be 'No' if:
 - any applicant is not an inventor
 - there is an inventor who is not an applicant, or
 - any applicant is a corporate body.

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Please sign here ➡

A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

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A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

Claim(s)

Description

Abstract

Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

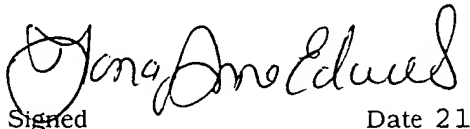
Patents Form 7/77 - Statement of Inventorship and Right to Grant (please state how many)

Patents Form 9/77 - Preliminary Examination/Search

Patents Form 10/77 - Request for Substantive Examination

9 Request

I/We request the grant of a patent on the basis of this application.




Signed

Date 21/08/2000

(day month year)

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Treatment of Wounds

This invention relates to the use of cyclic guanosine 3', 5'-monophosphate type five (cGMP PDE5) inhibitors (hereinafter PDE5 inhibitors), including in particular the
5 compound sildenafil, for the treatment of chronic wounds including in particular chronic venous ulcers, chronic decubitus (pressure sores) and arterial ulcers; and acute wounds.

Chronic wounds, by definition, take a long time to heal. Part of the process of repair requires a good blood supply and a pro-healing environment that allow the healing
10 process to occur. Typical phases in the healing of a wound include haemostasis, inflammation, repair and regeneration and finally re-modeling. In a chronic wound, one or more of these mechanism is impaired.

The method of treating a wound depends on its type.

15 Chronic venous ulcers, also known as venous leg ulcers or venous stasis ulcers, common in patients with venous insufficiency, are characterised by increased healing time and resistance to treatment. They are treated by simply applying the appropriate dressing and applying a compressive bandage.

20 Chronic arterial ulcers are caused typically by plaque in the arteries which lead to blockage and impaired blood supply. They heal slowly because of poor oxygen supply and nutrition. Treatment requires support and re-vascularisation if possible.

25 Chronic decubitus ulcers or pressure sores are caused by exerting pressure on an area of the body for extended periods, typically longer than 3 hours. Decubitus ulcers are treated by dressing the wound and removing the pressure. If the sore is small enough then the sores can be closed surgically.

30 Acute wounds, e.g. cuts and grazes to the skin, are treated by simply keeping the wound clean and dry. In young, healthy individuals the rate of healing is rapid. However, in the elderly or immunocompromised healing can be prolonged. Healing will also be prolonged if the wound becomes infected.

There is some suggestion in the literature that nitric oxide improves the rate of wound healing.

It is known that cGMP PDE5 inhibitors increase intracellular concentrations of nitric oxide derived cGMP, thereby enhancing the effect of nitric oxide, which is responsible for the efficacy of sildenafil in the treatment of male erectile dysfunction.

We have found elevated levels of the enzyme cGMP PDE5 in wounded tissue. In particular, where the tissue is inflamed or scarred.

10

No therapeutic agent is currently available which increases the rate of healing of these wound types.

According to a first aspect, the invention provides a method of treating wounds in a patient which comprises treating the patient with an effective amount of a cGMP PDE5 inhibitor, or a pharmaceutical composition thereof, wherein the wound type is selected from: chronic venous ulcers, chronic arterial ulcers, chronic debuticus and acute wounds.

15

According to a second aspect, the invention provides the use of a cGMP PDE5 inhibitor for the manufacture of a medicament for the treatment of wounds, selected from the following types: chronic venous ulcers, chronic arterial ulcers, chronic debuticus and acute wounds.

20

Suitable cGMP PDE5 inhibitors for the use according to the present invention include:

25

the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0463756; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0526004; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 93/06104; the isomeric pyrazolo [3,4-d]pyrimidin-4-ones disclosed in published international patent application WO 93/07149; the quinazolin-4-ones disclosed in published international patent application WO 93/12095; the pyrido [3,2-d]pyrimidin-4-ones disclosed in published international patent application WO 94/05661; the purin-6-ones disclosed in published international patent application WO 94/00453; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 98/49166; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 99/54333;

30

35

the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995751; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 00/24745; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995750; the compounds disclosed in published international application WO95/19978; the compounds disclosed in published international application WO 99/24433 and the compounds disclosed in published international application WO 93/07124.

It is to be understood that the contents of the above published patent applications, and in particular the general formulae and exemplified compounds therein are incorporated herein in their entirety by reference thereto.

Preferred type V phosphodiesterase inhibitors for the use according to the present invention include:

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine (see EP-A-0463756);

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see EP-A-0526004);

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO98/49166);

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO99/54333);

(+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 3-ethyl-5-[5-[4-ethylpiperazin-1-ylsulphonyl]-2-(((1R)-2-methoxy-1-methylethyl)oxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one (see WO99/54333);

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 1-{6-ethoxy-5-[3-ethyl-6,7-

dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulphonyl)-4-ethylpiperazine (see Example 1 hereinafter);

5 5-[2-iso-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see Example 2 hereinafter);

10 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see Example 3 hereinafter);
(6R, 12aR)-2,3,6,7, 12, 12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) - pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351), i.e. the compound of examples 78 and 95 of published international application WO95/19978, as well as the compound of examples 1, 3, 7 and 8;

15 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil) also known as 1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulphonyl]-4-ethylpiperazine, i.e. the compound of examples 20, 19, 337 and 336 of published international application
20 WO99/24433;

the compound of example 11 of published international application WO93/07124 (EISAI);
and

25 compounds 3 and 14 from Rotella D P, *J. Med. Chem.*, **2000**, 43, 1257.

Still other type cGMP PDE5 inhibitors useful in conjunction with the present invention include: 4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazoliny]-4-
30 piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent-4,5]imidazo[2,1-b]purin-4(3H)one; furazlocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]-imidazo[2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-
35 chlorophenyl) propoxy)-3-(2H)pyridazinone; 1-methyl-5(5-morpholinoacetyl)-2-n-

propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo(4,3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); E-8010 and E-4010 (Eisai); Bay-38-3045 & 38-9456 (Bayer) and Sch-51866.

The suitability of any particular cGMP PDE5 inhibitor can be readily determined by evaluation of its potency and selectivity using literature methods followed by evaluation of its toxicity, absorption, metabolism, pharmacokinetics, etc in accordance with standard pharmaceutical practice.

Preferably, the cGMP PDE5 inhibitors have an IC₅₀ at less than 100 nanomolar, more preferably, at less than 50 nanomolar, more preferably still at less than 10 nanomolar.

IC₅₀ values for the cGMP PDE5 inhibitors may be determined using established literature methodology, for example as described in EP0463756-B1 and EP0526004-A1.

Preferably the cGMP PDE5 inhibitors used in the invention are selective for the PDE5 enzyme. Preferably they are selective over PDE3, more preferably over PDE3 and PDE4. Preferably, the cGMP PDE5 inhibitors of the invention have a selectivity ratio greater than 100 more preferably greater than 300, over PDE3 and more preferably over PDE3 and PDE4.

Selectivity ratios may readily be determined by the skilled person. IC₅₀ values for the PDE3 and PDE4 enzyme may be determined using established literature methodology, see S A Ballard *et al*, Journal of Urology, 1998, vol. 159, pages 2164-2171.

The cGMP PDE5 inhibitors can be administered alone but, in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the cGMP PDE5 inhibitors can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions,

which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium
5 citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropylcellulose, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic
10 acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the
15 cGMP PDE5 inhibitors of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

20 The cGMP PDE5 inhibitors can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The
25 aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

30 The dosage of cGMP PDE5 inhibitor in such formulations will depend on its potency, but can be expected to be in the range of from 1 to 500 mg for administration up to three times a day. For oral and parenteral administration to human patients, the daily dosage level of the cGMP PDE5 inhibitor will usually be from 5 to 500 mg (in single or divided doses). In the case of sildenafil, a preferred dose is in the range 10 to 100 mg which can
35 be administered up to three times a day. However the precise dose will be as determined

by the prescribing physician and will depend on the age and weight of the patient and severity of the symptoms.

Thus, for example, tablets or capsules of the cGMP PDE5 inhibitor may contain from 5 to 250 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The cGMP PDE5 inhibitors can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the cGMP PDE5 inhibitor, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the cGMP PDE5 inhibitor and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of the cGMP PDE5 inhibitor, for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the cGMP PDE5 inhibitors can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The cGMP PDE5 inhibitors may also be dermally or transdermally administered, for example, by the use of a skin patch.

For application topically to the skin, the cGMP PDE5 inhibitors can be formulated as a suitable ointment containing the inhibitor suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

- 10 The cGMP PDE5 inhibitors may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

- 20 Generally, in humans, oral administration of the cGMP PDE5 inhibitors is the preferred route, being the most convenient. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, sublingually or buccally.

- 25 The cGMP PDE5 inhibitors can also be administered in combination with other active agents. For example:

- a) one or more naturally occurring or synthetic prostaglandins or esters thereof. Suitable prostaglandins for use herein include compounds such as alprostadil, prostaglandin E₁, prostaglandin E₀, 13, 14 - dihydroprosta glandin E₁, prostaglandin E₂, eprostinol, natural synthetic and semi-synthetic prostaglandins and derivatives thereof including those described in US 6,037,346 issued on 14th March 2000 and incorporated herein by reference, PGE₀, PGE₁, PGA₁, PGB₁, PGF₁ α, 19-hydroxy PGA₁, 19-hydroxy - PGB₁, PGE₂, PGB₂, 19-hydroxy-PGA₂, 19-hydroxy-PGB₂,

PGE₃α, carboprost tromethamine dinoprost, tromethamine, dinoprostone, lipo prost, gemeprost, metenoprost, sulprostune, tiaprost and moxislyate; and/or

- b) one or more α - adrenergic receptor antagonist compounds also known as α -
 5 adrenoceptors or α-receptors or α-blockers. Suitable compounds for use herein include: the α-adrenergic receptors as described in PCT application WO99/30697 published on 14th June 1998, the disclosures of which relating to α-adrenergic receptors are incorporated herein by reference and include, selective α₁-adrenoceptors or α₂-adrenoceptors and non-selective adrenoceptors, suitable α₁-
 10 adrenoceptors include: phentolamine, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, dapiprazole, phenoxybenzamine, idazoxan, efaraxan, yohimbine, rauwolfia alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, terazosin, abanoquil and prazosin; α₂-blockers from US 6,037,346 [14th March 2000] dibenamine,
 15 tolazoline, trimazosin and dibenarnine; α-adrenergic receptors as described in US patents: 4,188,390; 4,026,894; 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063; 3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference; α₂-Adrenoceptors include: clonidine, papaverine, papaverine hydrochloride, optionally in the presence of a cariotonic agent such as
 20 pirxamine; and/or
- c) one or more NO-donor (NO-agonist) compounds. Suitable NO-donor compounds for use herein include organic nitrates, such as mono- di or tri-nitrates or organic nitrate esters including glyceryl brinitrate (also known as nitroglycerin), isosorbide
 25 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside (SNP), 3-morpholinosydnonimine molsidomine, S-nitroso- N-acetyl penicilliamine (SNAP) S-nitroso-N-glutathione (SNO-GLU), N-hydroxy - L-arginine, amylnitrate, linsidomine, linsidomine chlorohydrate, (SIN-1) S-nitroso - N-cysteine, diazenium diolates, (NONOates), 1,5-pentanedinitrate, L-
 30 arginine, ginseng, zizphi fructus, molsidomine, Re - 2047, nitrosylated maxisylte derivatives such as NMI-678-11 and NMI-937 as described in published PCT application WO 0012075 ; and/or

- d) one or more potassium channel openers. Suitable potassium channel openers for use herein include nicorandil, cromokalim, levcromakalim, lemakalim, pinacidil, cliazoxide, minoxidil, charybdotoxin, glyburide, 4-aminopyridine, BaCl₂; and/or
- 5 e) one or more dopaminergic agents. Suitable dopaminergic compounds for use herein include D₂-agonists such as, pramipexol; apomorphine; and/or
- f) one or more vasodilator agents. Suitable vasodilator agents for use herein include nimodipine, pinacidil, cyclandelate, isoxsuprine, chlorpromazine, halo peridol,
10 Rec 15/2739, trazodone, pentoxifylline; and/or
- g) one or more thromboxane A₂ agonists; and/or
- h) one or more CNS active agents; and/or
- 15 i) one or more ergot alkaloids; Suitable ergot alkaloids are described in US patent 6,037,346 issued on 14th March 2000 and include acetergamine, brazergoline, bromerguride, cianergoline, delorgotril, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotril, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride, terguride;
20 and/or
- j) one or more compounds which modulate the action of atrial natriuretic factor (also known as atrial natriuretic peptide), such as inhibitors or neutral endopeptidase;
25 and/or
- k) one or more compounds which inhibit angiotensin-converting enzyme such as enalapril, and combined inhibitors of angiotensin-converting enzyme and neutral endopeptidase such as omapatrilat; and/or
- 30 l) one or more angiotensin receptor antagonists such as losartan; and/or
- m) one or more substrates for NO-synthase, such as L-arginine; and/or
- 35 n) one or more calcium channel blockers such as amlodipine; and/or

- o) one or more antagonists of endothelin receptors and inhibitors of endothelin-converting enzyme; and/or
- 5 p) one or more cholesterol lowering agents such as statins and fibrates; and/or
- q) one or more antiplatelet and antithrombotic agents, e.g. tPA, uPA, warfarin, hirudin and other thrombin inhibitors, heparin, thromboplastin activating factor inhibitors; and/or
- 10 r) one or more insulin sensitising agents such as rezulin and hypoglycaemic agents such as glipizide; and/or
- s) L-DOPA or carbidopa; and/or
- 15 t) one or more acetylcholinesterase inhibitors such as donezipil; and/or
- u) one or more steroidal or non-steroidal anti-inflammatory agents; and/or
- 20 v) one or more matrix metalloproteases (MMP), particularly MMP-3, MMP-12 and MMP-13; and/or
- w) one or more urokinase inhibitors (uKA).
- 25 Particularly preferred agents for use in combination with the PDE5 inhibitors of the invention for treating wounds are one or more matrix metalloproteases (MMP), particularly MMP-3, MMP-12 and MMP-13; and/or one or more urokinase inhibitors (uKA).
- 30 It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention. Active ingredient means a cGMP PDE5 inhibitor.

Formulation 1: A tablet is prepared using the following ingredients :

	Weight (mg)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665

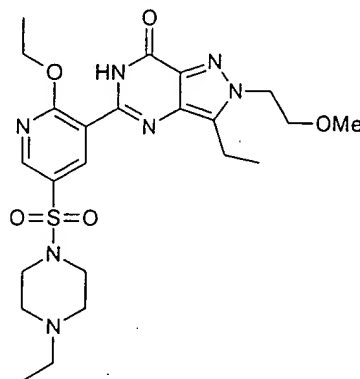
the components are blended and compressed to form tablets each weighing 665mg.

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Formulation 2 : An intravenous formulation may be prepared by combining active ingredient (100 mg) with isotonic saline (1000 ml)

Example 1

- 10 2-(Methoxyethyl)-5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

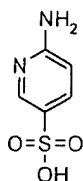


- A mixture of the product from stage i) below (0.75mmol), potassium bis(trimethylsilyl)amide (298mg, 1.50mmol) and ethyl acetate (73 microlitres, 0.75mmol) in ethanol (10ml) was heated at 120°C in a sealed vessel for 12 hours. The cooled mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, and the layers separated. The organic phase was dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol (98:2) as eluant to afford the title compound, 164mg;
- 20 Found : C, 53.18; H, 6.48; N, 18.14; C₂₃H₃₃N₇O₅S; 0.20C₂H₅CO₂CH₃ requires C, 53.21; H, 6.49; N, 18.25%; δ (CDCl₃) : 1.04 (3H, t), 1.40 (3H, t), 1.58 (3H, t), 2.41 (2H, q), 2.57 (4H,

m), 3.08 (2H, q), 3.14 (4H, m), 3.30 (3H, s), 3.92 (2H, t), 4.46 (2H, t), 4.75 (2H, q), 8.62 (1H, d), 9.04 (1H, d), 10.61 (1H, s); LRMS : m/z 520 ($M+1$)⁺; mp 161-162°C.

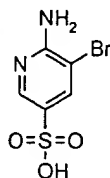
Preparation of Starting Materials

5 a) Pyridine-2-amino-5-sulphonic acid



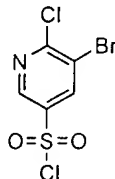
2-Aminopyridine (80g, 0.85mol) was added portionwise over 30 minutes to oleum (320g) and the resulting solution heated at 140°C for 4 hours. On cooling, the reaction was poured onto ice (200g) and the mixture stirred in an ice/salt bath for a further 2 hours. The resulting suspension was filtered, the solid washed with ice water (200ml) and cold IMS (200ml) and dried under suction to afford the title compound as a solid, 111.3g; LRMS : m/z 175 ($M+1$)⁺.

10 b) Pyridine-2-amino-3-bromo-5-sulphonic acid

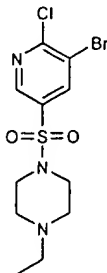


15 Bromine (99g, 0.62mol) was added dropwise over an hour, to a hot solution of the product from stage a) (108g, 0.62mol) in water (600ml) so as to maintain a steady reflux. Once the addition was complete the reaction was cooled and the resulting mixture filtered. The solid was washed with water and dried under suction to afford the title compound, 53.4g; δ (DMSO-d₆, 300MHz): 8.08 (1H, s), 8.14 (1H, s); LRMS : m/z 253 (M)⁺.

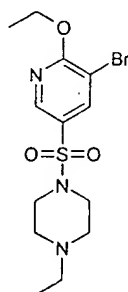
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c) Pyridine-3-bromo-2-chloro-5-sulphonyl chloride

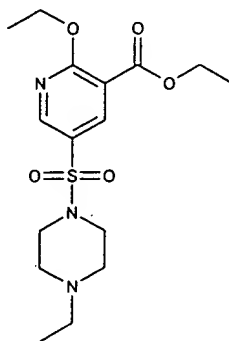
A solution of sodium nitrite (7.6g, 110.0mmol) in water (30ml) was added dropwise to an ice-cooled solution of the product from stage b) (25.3g, 100.0mmol) in aqueous hydrochloric acid (115ml, 20%), so as to maintain the temperature below 6°C. The reaction was stirred for 30 minutes at 0°C and for a further hour at room temperature. The reaction mixture was evaporated under reduced pressure and the residue dried under vacuum at 70°C for 72 hours. A mixture of this solid, phosphorus pentachloride (30.0g, 144mmol) and phosphorus oxychloride (1ml, 10.8mmol) was heated at 125°C for 3 hours, and then cooled. The reaction mixture was poured onto ice (100g) and the resulting solid filtered, and washed with water. The product was dissolved in dichloromethane, dried (MgSO₄), and evaporated under reduced pressure to afford the title compound as a yellow solid, 26.58g; δ (CDCl₃, 300MHz) : 8.46 (1H, s), 8.92 (1H, s).

d) 3-Bromo-2-chloro-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine

A solution of 1-ethylpiperazine (11.3ml, 89.0mmol) and triethylamine (12.5ml, 89.0mmol) in dichloromethane (150ml) was added dropwise to an ice-cooled solution of the product from stage c) (23.0g, 79.0mmol) in dichloromethane (150ml) and the reaction stirred at 0°C for an hour. The reaction mixture was concentrated under reduced pressure and the residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (99:1 to 97:3) to afford the title compound as an orange solid, 14.5g; δ (CDCl₃, 300MHz) : 1.05 (3H, t), 2.42 (2H, q), 2.55 (4H, m), 3.12 (4H, m), 8.24 (1H, s), 8.67 (1H, s).

e) 3-Bromo-2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine

A mixture of the product from stage d) (6.60g, 17.9mmol) and sodium ethoxide (6.09g, 89.55mmol) in ethanol (100ml) was heated under reflux for 18 hours, then cooled. The reaction mixture was concentrated under reduced pressure, the residue partitioned between water (100ml) and ethyl acetate (100ml), and the layers separated. The aqueous phase was extracted with ethyl acetate (2x100ml), the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a brown solid, 6.41g; Found : C, 41.27; H, 5.33; N, 11.11. C₁₃H₂₀BrN₃O₃S requires C, 41.35; H, 5.28; N, 10.99%; δ (CDCl₃, 300MHz) : 1.06 (3H, t), 1.48 (3H, t), 2.42 (2H, q), 2.56 (4H, m), 3.09 (4H, m), 4.54 (2H, q), 8.10 (1H, s), 8.46 (1H, s); LRMS : m/z 378, 380 (M+1)⁺.

f) Pyridine 2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-3-carboxylic acid ethyl ester

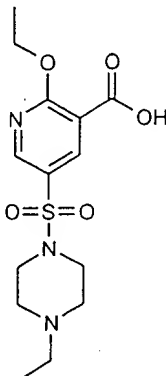
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A mixture of the product from stage e) (6.40g, 16.92mmol), triethylamine (12ml, 86.1mmol); and palladium (0) tris(triphenylphosphine) in ethanol (60ml) was heated at 100°C and 200 psi, under a carbon monoxide atmosphere, for 18 hours, then cooled. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 97:3) to afford the title compound as an orange oil, 6.2g; δ (CDCl₃, 300MHz) : 1.02 (3H, t), 1.39 (3H, t), 1.45 (3H, t),

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2.40 (2H, q), 2.54 (4H, m), 3.08 (4H, m), 4.38 (2H, q), 4.55 (2H, q), 8.37 (1H, s), 8.62 (1H, s); LRMS : m/z 372 (M+1)⁺

g) Pyridine 2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-3-carboxylic acid



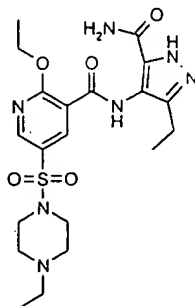
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A mixture of the product from stage f) (4.96g, 13.35mmol) and aqueous sodium hydroxide solution (25ml, 2N, 50.0mmol) in ethanol (25ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to half it's volume, washed with ether and acidified to pH 5 using 4N hydrochloric acid. The aqueous solution was extracted with dichloromethane (3x30ml), the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a tan coloured solid, 4.02g; δ (DMSO-d₆, 300MHz): 1.18 (3H, t), 1.37 (3H, t), 3.08 (2H, q), 3.17-3.35 (8H, m), 4.52 (2H, q), 8.30 (1H, s), 8.70 (1H, s).

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h) 4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-1H-3-ethylpyrazole-5-carboxamide

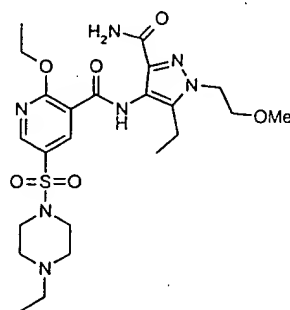


A solution of 3-ethyl-1H-pyrazole-5-carboxamide (WO 9849166) (9.2g, 59.8mmol) in N,N-dimethylformamide (60ml) was added to a solution of the product from stage g) (21.7g, 62.9mmol), 1-hydroxybenzotriazole hydrate (10.1g, 66.0mmol)

20

and triethylamine (13.15ml, 94.3mmol) in dichloromethane (240ml). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (13.26g, 69.2mmol) was added and the reaction stirred at room temperature for 6 hours. The dichloromethane was removed under reduced pressure, the remaining solution poured into ethyl acetate (400ml), and this mixture washed with aqueous sodium bicarbonate solution (400ml). The resulting crystalline precipitate was filtered, washed with ethyl acetate and dried under vacuum, to afford the title compound, as a white powder, 22g; δ (CDCl_3 +1 drop DMSO-d_6) 0.96 (3H, t), 1.18 (3H, t), 1.50 (3H, t), 2.25-2.56 (6H, m), 2.84 (2H, q), 3.00 (4H, m), 4.70 (2H, q), 5.60 (1H, br s), 6.78 (1H, br s), 8.56 (1H, d), 8.76 (1H, d), 10.59 (1H, s), 12.10-12.30 (1H, s); LRMS: m/z 480 (M+1)*.

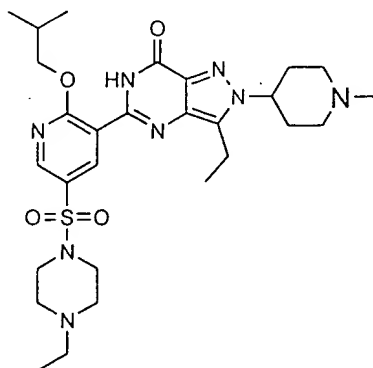
- i) 2-Methoxyethyl-4-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethylpyrazole-5-carboxamide



1-Bromo-2-methoxyethane (1.72mmol) was added to a solution of the product from stage h) (750mg, 1.56mmol) and caesium carbonate (1.12g, 3.44mmol) in N,N-dimethylformamide (15ml) and the reaction stirred at 60°C for 18 hours. The cooled mixture was partitioned between water and ethyl acetate, and the layers separated. The organic layer was dried (MgSO_4), concentrated under reduced pressure and azeotroped with toluene to give a solid. This product was recrystallised from ether, to afford the title compound as a white solid.

Example 2

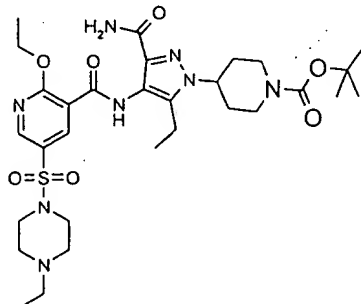
5-[2-iso-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



- 5 A mixture of the product from stage b) below (90mg, 0.156mmol), potassium bis(trimethylsilyl)amide (156mg, 0.78mmol) and ethyl acetate (14mg, 0.156mmol) in iso-propanol (12ml) was stirred at 130°C for 6 hours in a sealed vessel. The cooled reaction mixture was poured into saturated aqueous sodium bicarbonate solution (60ml), and extracted with ethyl acetate (60ml). The combined organic extracts were dried (MgSO₄),
- 10 and evaporated under reduced pressure to give a gum. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (92.6:6.6:0.6) to afford the title compound as a beige foam, 36 mg; δ (CDCl₃) 1.01 (3H, t), 1.12 (6H, d), 1.39 (3H, t), 1.94 (2H, m), 2.15 (2H, m), 2.22-2.44 (6H, m), 2.55 (6H, m), 3.02 (4H, m), 3.14 (4H, m), 4.22 (1H, m), 4.43 (2H, d), 8.60 (1H, d), 9.00 (1H, d), 10.54
- 15 (1H, s).

Preparation of Starting Materials

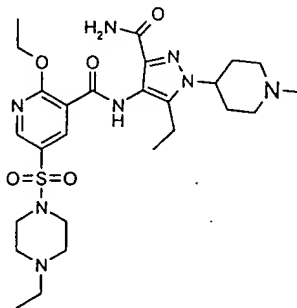
- a) 2-(1-tert-Butoxycarbonylpiperidin-4-yl)-4-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethylpyrazole-5-carboxamide



Sodium hydride (64mg, 60% dispersion in mineral oil, 1.6mmol) was added to a solution of the product from Example 1, stage h) (1.46mmol) in tetrahydrofuran

(10ml), and the solution stirred for 10 minutes. *tert*-Butyl 4-[(methanesulphonyl)oxy]-1-piperidinecarboxylate (WO 9319059) (1.60mmol) was added and the reaction stirred at 60°C for 3 days. The cooled mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, and the phases separated. The aqueous layer was extracted with ethyl acetate, the combined organic solutions dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol (98:2) as eluant to afford the title compound as a white foam, 310 mg; δ (CDCl₃) 1.02 (3H, t), 1.23 (3H, t), 1.49 (9H, s), 1.57 (3H, m), 1.93 (2H, m), 2.16 (2H, m), 2.40 (2H, q), 2.54 (4H, m), 2.82-2.97 (4H, m), 3.10 (4H, m), 4.30 (3H, m), 4.79 (2H, q), 5.23 (1H, s), 6.65 (1H, s), 8.63 (1H, d), 8.82 (1H, d), 10.57 (1H, s).

- b) 4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethyl-2-(1-methylpiperidin-4-yl)pyrazole-5-carboxamide



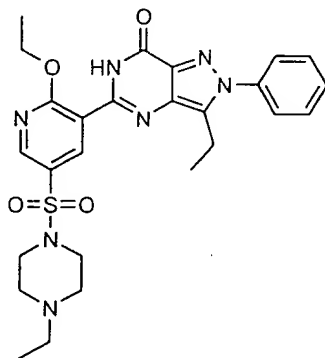
Trifluoroacetic acid (1.5ml) was added to a solution of the product from stage a) above (320mg, 0.48mmol) in dichloromethane (2ml) and the solution stirred at room temperature for 2 ½ hours. The reaction mixture was evaporated under reduced pressure and the residue triturated well with ether and dried under vacuum, to provide a white solid. Formaldehyde (217 microlitres, 37% aqueous, 2.90mmol) was added to a solution of the intermediate amine in dichloromethane (8ml), and the solution stirred vigorously for 30 minutes. Acetic acid (88 microlitres, 1.69mmol) was added, the solution stirred for a further 30 minutes, then sodium triacetoxyborohydride (169mg, 0.80mmol) was added and the reaction stirred at room temperature for 16 hours. The reaction mixture was poured into aqueous sodium bicarbonate solution, and extracted with ethyl acetate. The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (91.75:7.5:0.75) as

eluant to afford the title compound, 70mg; δ (CDCl₃) 1.02 (3H, t), 1.22 (3H, t), 1.58 (3H, t), 1.92 (2H, m), 2.14 (2H, m), 2.25-2.45 (7H, m), 2.54 (4H, m), 2.91 (2H, q), 2.99-3.16 (6H, m), 4.08 (1H, m), 4.78 (2H, q), 5.11 (1H, br s), 6.65 (1H, br s), 8.63 (1H, d), 8.83 (1H, d), 10.53 (1H, s).

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Example 3

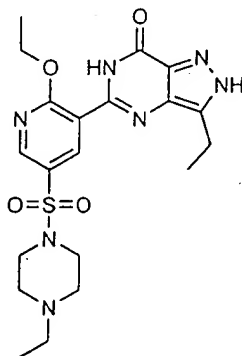
5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



- 10 Pyridine (0.1ml, 1.08mmol) was added to a mixture of the product from stage a) below (250mg, 0.54mmol), copper (II) acetate monohydrate (145mg, 0.72mmol), benzenboronic acid (132mg, 1.08mmol) and 4Å molecular sieves (392mg) in dichloromethane (5ml), and the reaction stirred at room temperature for 4 days. The reaction mixture was filtered and the filtrate evaporated under reduced pressure. The
- 15 crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (97:3:0.5) as eluant, and triturated with ether:hexane. The resulting solid was filtered and recrystallised from *iso*-propanol:dichloromethane to give the title compound as a solid, 200mg, δ (CDCl₃) 1.02 (3H, t), 1.47 (3H, t), 1.60 (3H, t), 2.42 (2H, q), 2.58 (4H, m), 3.10 (2H, q), 3.17 (4H, m),
- 20 4.76 (2H, q), 7.40 (1H, m), 7.51 (2H, m), 7.80 (2H, d), 8.67 (1H, d), 9.16 (1H, s), 10.90 (1H, s); LRMS : m/z 538 (M+1)*.

Preparation of Starting Materials

- a) 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



- 5 Potassium bis(trimethylsilyl)amide (8.28g, 41.6mmol) was added to a solution of the product from Example 1, stage h) (10.0g, 20.8mmol) and ethyl acetate (2ml, 20mmol) in ethanol (160ml), and the reaction mixture heated at 120°C for 12 hours in a sealed vessel. The cooled mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant, to give the title compound, 3.75g; δ (CDCl₃) 1.03 (3H, t), 1.42 (3H, t), 1.60 (3H, t), 2.42 (2H, q), 2.58 (4H, m), 3.02 (2H, q), 3.16 (4H, m), 4.78 (2H, q), 8.66 (1H, d), 9.08 (1H, d), 11.00 (1H, s) 11.05-11.20 (1H, br s), LRMS : m/z 462 (M+1)⁺.

Claims

- 1 A method of treating wounds in a patient which comprises treating the patient with
an effective amount of a cGMP PDE5 inhibitor, or a pharmaceutical composition
5 thereof, wherein the wound type is selected from: chronic venous ulcers, chronic
arterial ulcers, chronic debuticus and acute wounds.
- 2 The use of a cGMP PDE5 inhibitor for the manufacture of a medicament for the
treatment of wounds, selected from the following types: chronic venous ulcers,
10 chronic arterial ulcers, chronic debuticus and acute wounds.
- 3 A method or use as claimed in claim 1 or claim 2 wherein the cGMP PDE5
inhibitor is sildenafil.

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